

National Phase of  
PCT/GB00/03681

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REMARKS

Claims 1-3, 8, 9, 22, 24-28, 31-36 and 38 have been amended.

Claim 23 remains unchanged.

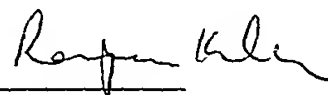
Claims 4-7, 10-21, 29, 30, 37 and 39 have been canceled.

A marked up clean version of the changes made to the claims by the current amendment is attached hereto. The attached page is captioned **Version with markings to show changes made.**

Applicants reserve the right to resubmit the canceled claims in Divisionals, Continuations and/or Continuations-in-part.

The enclosed filing fee has been calculated based on the amended claims. If any additional fee is due, please charge to Deposit Account No. 08-2442.

Respectfully submitted,  
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**Version with markings to show changes made.**

1. (Amended) A method of inhibiting secretion from a non-neuronal inflammatory cell comprising administering an agent comprising at least first and second domains, wherein the first domain cleaves one or more proteins essential to exocytosis and the second domain translocates the first domain into the inflammatory cell.
2. (Amended) A method according to Claim 1, for treatment of disease caused, exacerbated or maintained by secretion from [a] said non-neuronal inflammatory cell [or non-neuronal cells].
3. (Amended) A method according to Claim 1 [or 2], wherein the agent further comprises a third domain for targeting the agent to [a] said non-neuronal inflammatory cell.

Claims 4-7 have been canceled.

8. (Amended) A method according to Claim [7] 3 wherein the third domain comprises [or consists of] a ligand selected from (i) for mast cells, complement receptors in general, including C4 domain of the Fc IgE, and antibodies/ligands to the C3a/C4a-R complement receptor; (ii) for eosinophils, antibodies/ligands to the C3a/C4a-R complement receptor, anti VLA-4 monoclonal antibody, anti-IL5 receptor, antigens or antibodies reactive toward CR4 complement receptor; (iii) for macrophages and monocytes, macrophage stimulating factor, (iv) for macrophages, monocytes and neutrophils, bacterial LPS and yeast B-glucans which bind to CR3, (v) for neutrophils, antibody to OX42, an antigen associated with the iC3b complement receptor, or IL8; (vi) for fibroblasts, mannose 6-phosphate/insulin-like growth factor-beta (M6P/IGF-II) receptor and PA2.26, antibody to a cell-surface receptor for active fibroblasts in mice.

9. (Amended) A method according to Claim [7 or 8] 2 for the treatment of a disease [caused, exacerbated, or maintained by secretion from an inflammatory cell, preferably for treatment of a disease selected from] selected from the group consisting of allergies (seasonal allergic rhinitis (hay fever), allergic conjunctivitis, vasomotor rhinitis and food allergy), eosinophilia, asthma, rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus, ulcerative colitis, Crohn's disease, haemorrhoids, pruritus, glomerulonephritis, hepatitis, pancreatitis, gastritis, vasculitis, myocarditis, psoriasis, eczema, chronic radiation-induced fibrosis, lung scarring and other fibrotic disorders.

Claims 10-21 have been canceled.

22. (Amended) A method according to [any previous] Claim 1, wherein the agent comprises a first domain that cleaves a protein selected from SNAP-25, synaptobrevin and syntaxin.

23. (Unchanged) A method according to Claim 22 wherein the first domain comprises a light chain of a clostridial neurotoxin, or a fragment, variant or derivative thereof which inhibits exocytosis.

24. (Amended) A method according to [any previous] Claim 1, wherein the second domain comprises a H<sub>N</sub> region of a clostridial polypeptide, or a fragment, variant or derivative thereof that translocates the exocytosis inhibiting activity of the first domain into the inflammatory cell.

25. (Amended) A method according to [any previous] Claim 1 for inhibition of constitutive and regulated release from non-neuronal inflammatory cells.

26. (Amended) An agent for inhibiting secretion from a non-neuronal inflammatory cell, comprising at least first, second and third domains, wherein the first domain cleaves one or more proteins essential to exocytosis, the second domain

translocates the first domain into the cell and the third domain binds to [a] said non-neuronal inflammatory cell.

27. (Amended) An agent according to Claim 26, wherein the third domain is as defined in [any of Claims] Claim 4 [, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, and 20].

28. (Amended) A pharmaceutical composition comprising an agent according to Claim 26 [or 27] in combination with a pharmaceutically acceptable carrier.

Claim 29 and 30 have been canceled.

31. (Amended) A nucleic acid construct encoding an agent according to Claim 26 [or 27], said construct comprising nucleic acid sequences encoding the first, second and third domains.

32. (Amended) A nucleic acid construct according to Claim 31, operably linked to promoter and terminator sequences, and optionally regulatory sequences, said promoter, terminator and regulatory sequences being functional in a non-neuronal inflammatory target cell to effect expression of said agent in said target cell.

33. (Amended) An agent for use in gene therapy, comprising a nucleic acid sequence encoding a first domain which cleaves one or more proteins essential to exocytosis, and a second domain associated with the nucleic acid sequence which, following administration to a patient, translocates the nucleic acid sequence into a non-neuronal inflammatory target cell and, when in said non-neuronal inflammatory target cell, expression of the nucleic acid sequence is effected therein.

34. (Amended) An agent according to Claim 33, wherein the nucleic acid sequence is operably linked to promoter and terminator sequences, and optionally regulatory sequences, said promoter, terminator and regulatory sequences being functional in the non-neuronal inflammatory target cell to effect expression of said

agent in said non-neuronal inflammatory target cell.

35. (Amended) An agent according to Claim [32 or] 33, wherein the agent further comprises a third domain for targeting the agent to said non-neuronal inflammatory cell.

36. (Amended) A method of treating by gene therapy a disease caused, exacerbated or maintained by secretion from a non-neuronal inflammatory cell, said method comprising administering to a patient an agent according to [any of Claims] Claim 33 [-35].

Claim 37 has been canceled.

38. (Amended) A method of treating a disease caused, exacerbated or maintained by secretion from a non-neuronal inflammatory cell, said method comprising administering to a patient a polypeptide that cleaves one or more proteins essential to exocytosis, or a nucleic acid encoding said polypeptide, to a patient.

Claim 39 has been canceled.